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Trace Elements and the Electroencephalogram During Long-term Lithium Treatment

NORMAN S. HARVEY, JOHN JARRATT and NEIL I. WARD

Endogenous bromine has been found to be raised during lithium treatment, and it has been suggested that it may augment the therapeutic effect of lithium. Our findings in a study of 12 patients and 12 controls support this contention. Electroencephalographic effects of bromine, vanadium and aluminium were studied – higher bromine and vanadium levels were associated with irregular cortical activity. Electroencephalographic abnormalities were associated with more side-effects of lithium.

It has been shown by Handorf *et al* (1985) and Campbell *et al* (1986) that bromine levels are higher in patients receiving lithium; these workers considered that the effect was most likely due to lithium interfering with the renal excretion of bromine. Handorf *et al* (1985) suggested that the relatively slight increase of bromine, in the subtherapeutic range, could have pharmacological effects worthy of further study. Bromine could contribute to the anti-manic effect of lithium, and lithium could potentiate the sedative effects of bromine. In the present study we, therefore, assessed whether the bromine levels of lithium patients were raised, and if so whether they related to response to lithium treatment.

Slightly raised levels of bromine in blood in workers using methyl bromide as a pesticide have been shown to produce electroencephalographic (EEG) abnormalities (Verberk *et al*, 1979). It is well known that long-term lithium treatment produces EEG abnormalities in some patients, although it is impossible to predict those in whom they will occur. Some workers have found a relationship between EEG changes and serum lithium levels (Mayfield & Brown, 1966), but Johnson *et al* (1970) found that EEG changes correlate more with lithium-induced side-effects than with serum lithium levels. Zakowska-Dabrowska & Rybakowski (1973) found that EEG changes tended to relate to lithium levels in red blood cells (RBCs) during established treatment. In view of the unresolved origin of EEG abnormalities associated with long-term lithium treatment, we tested whether these abnormalities were contributed to by associated disturbances of trace elements.

In addition to our interest in bromine, we have recently found that RBC vanadium levels appear to be raised by lithium (Harvey & Ward, 1991). Also, some early blood results from our lithium clinic showed that the mean ratio of RBC: serum aluminium of lithium patients, whose cognition was assumed to be normal, was considerably higher than that reported in dialysis patients (Van der Voet & de Wolff, 1985), and serum aluminium has been shown to be raised in patients receiving lithium (Campbell *et al*, 1989). Aluminium toxicity causes mild slowing of the dominant EEG rhythm with bursts of high-voltage delta activity frontally, at times accompanied by spike activity (Alfrey, 1985). This picture is similar to that caused by lithium.

In view of the above findings the present study examines the relationships of EEG abnormalities with bromine, vanadium and aluminium during lithium treatment. We have measured the serum and RBC levels, and are not aware of RBC trace elements having been studied in psychiatric patients before. The circumstances of the project permitted only a relatively small number of patients to be involved in what amounts to a pilot study.

Method

Twelve long-term lithium out-patients from an earlier study were recruited to follow-up studies, including the present work. Their DSM-III-R diagnoses were of bipolar disorder or major depression, recurrent (American Psychiatric Association, 1987). They were in remission and none had alcohol problems. In addition to lithium, two were receiving tricyclic antidepressants. Throughout the study no attempts were made to influence dietary intake.

Subjects were given the Symptom Checklist questionnaire (Ghose, 1977), which produces a score consisting of the sum of the lithium-induced side-effects, weighted according to severity. On a later visit they were assessed for intelligence (Weschler, 1981), a blood sample was taken for lithium determination, then an EEG was performed, without photic stimulation or over-breathing. The two patients on antidepressants had discontinued this treatment in the week before the EEG. These tests were given in the same order, in the same laboratory, and all but one were commenced at approximately 10 a.m. The patients remained alert throughout the test procedures.

Blood specimens were taken some weeks later for trace-element analysis and haematocrit determination, at which time nine patients were still receiving lithium, one of whom

was receiving amitriptyline and another prochlorperazine. Similar specimens were taken from a matched group of 12 normal control subjects comprised primarily of the relatives of general-hospital patients, as well as normal subjects undergoing routine blood checks and hospital staff members. Their mean (s.d.) age was 58.8 (11.3) years compared with 58.1 (12.3) years for the patient group. The male:female ratio was 1:3 for each group. The normal controls were not suffering from any medical disorder, were on no special diet or dietary supplements, were not on any medication, and had a restricted intake of alcohol. All specimens were collected in metal-free polypropylene test-tubes and subjected to inductively coupled plasma source mass spectrometry (ICP-MS) (Ward *et al*, 1989) to determine levels of trace elements in serum and whole blood.

The blood fractions were transferred into 15 ml metal-free polypropylene containers (Elkay Lab. Products, Hampshire, UK), and weighed. Next, 1 ml of concentrated nitric acid (Pronalys grade, BDH Chemicals Ltd, Essex, UK) was added to each tube. These samples were then wet digested in a water bath at 100 °C for 6 hours. The digested samples were made up to 2 ml volumes with the addition of double-distilled deionised water. All samples were analysed using a Plasmaquad IPC-MS instrument (VG Elemental Ltd, Winsford, Cheshire, UK). Multi-elemental scan conditions were used, with quality-control checks using internal sensitivity standards and accuracy validation against the NIST SRM 909 human serum certified reference material (National Institute of Standards and Technology, Gaithersburg, USA).

The haematocrit determinations were performed on a Coulter S Plus machine. The RBC levels of the trace elements were calculated from the serum and whole-blood levels and the haematocrit (Summerton *et al*, 1989). Some of our data on the effect of lithium on trace elements, including vanadium, are published elsewhere (Harvey & Ward, 1991).

The patients' clinical histories were obtained from their records, and any relapses in the two years following the tests were assessed prospectively.

The EEGs were analysed by a clinical neurophysiologist blind to the rest of the study (JJ). Of the nine patients receiving lithium at the time of trace-element testing, JJ identified five with prominent EEG abnormalities, including slowing of the dominant frequency, irregular delta activity, bursts of fairly rhythmic slow activity and, in one of them, some sharp waveforms. Rhythmic slow waves, consistent with a subcortical origin, were found in four of the five patients with prominent changes. Examples of these four types of abnormality, together with a tracing from one of the less abnormal group, are shown in Fig. 1. These findings were used to subdivide the patients into two groups, those with or without marked EEG abnormalities, which were compared. Of the four patients with less abnormal records, three showed irregular slow activity, consistent with a cortical origin, but none showed evidence of subcortical episodes.

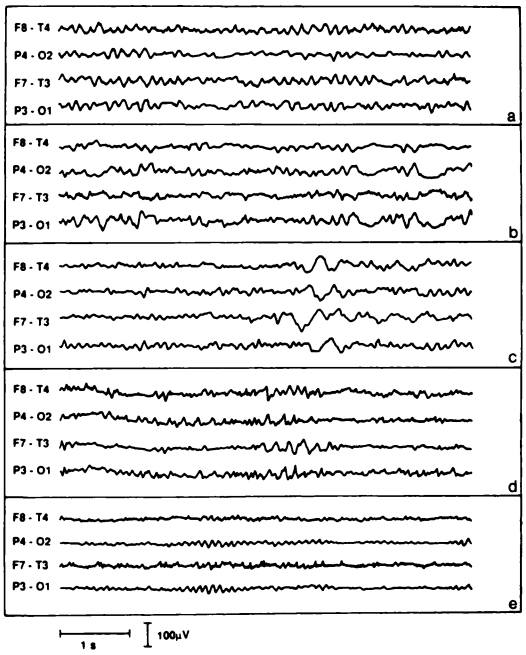

Fig. 1(a) Slowed dominant rhythm, (b) irregular delta activity, (c) bursts of fairly rhythmic slow activity, (d) sharp waveforms, (e) mild excess background slow activity.

Results

Raised bromine levels were confirmed in the patients receiving lithium, in serum and the RBCs, without any disturbance of the RBC:serum bromine ratio (Table 1). The aluminium levels were normal and the levels of vanadium were raised (Table 1).

Table 1
Mean (s.d.) levels of bromine, aluminium and vanadium among patients on lithium v. controls

	Patients ($n=9$)	Controls ($n=9$)	P (2-tailed paired t-test)
Bromine: μg/ml			
serum	6.66 (0.84)	4.80 (0.59)	<0.002
RBC	4.93 (1.41)	3.87 (0.58)	<0.05
RBC:serum ratio	0.74 (0.19)	0.81 (0.11)	NS
Aluminium: ng/ml			
serum	1.73 (0.62)	2.07 (0.68)	NS
RBC	12.59 (4.94)	12.12 (3.52)	NS
RBC:serum ratio	7.79 (3.54)	6.25 (1.80)	NS
Vanadium: ng/ml			
serum	0.40 (0.15)	0.20 (0.06)	<0.004
RBC	3.54 (1.58)	1.13 (0.22)	<0.003
RBC:serum ratio	9.45 (4.47)	5.92 (1.52)	<0.04

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Table 2
Spearman's correlations and two-tailed P values for relations between lithium treatment and serum and RBC bromine levels

	Dose of lithium	Serum lithium level	RBC lithium level	Duration of treatment
Serum bromine level	0.736 $P<0.004$	0.559 $P<0.03$	0.713 $P<0.006$	0.753 $P<0.003$
RBC bromine level	0.514 $P<0.05$	0.461 $P<0.07$	0.587 $P<0.03$	0.641 $P<0.02$

For the entire patient group the dose of lithium, serum lithium concentration, RBC lithium and duration of lithium treatment were correlated with serum bromine and RBC bromine (Table 2), the results suggesting that raised bromine levels are dependent on the amount of lithium ingested. Among the nine patients still taking lithium at the time the blood specimens were taken, serum bromine was negatively related to the number of relapses while on lithium, assessed retrospectively, ($r=-0.782$, two-tailed $P<0.007$).

To eliminate treatment selection bias, we used the relative relapse rate for lithium (RRL), calculated as the ratio of the relapse rate while on lithium to the relapse rate before lithium was started. There was a mean (s.d.) of 7.9 (5.8) relapses over the entire duration of the illness, which had lasted 18.3 (7.2) years. During a mean (s.d.) treatment time of 10.4 (3.8) years, 0.7 (0.4) relapses occurred. We found that serum bromine related negatively to the RRL ($n=9$, $r=-0.650$, two-tailed $P<0.03$). There was no relationship between serum or RBC lithium and number of relapses or RRL.

At the two-year follow-up, four of the nine patients remaining on lithium had relapsed. As predicted, these relapsers had a lower mean (s.d.) serum bromine level than the non-relapsers (6.1 (0.46) μg/ml v. 7.1 (0.83) μg/ml, $t=2.27$, one-tailed $P<0.04$). Again, there was no significant difference in the lithium levels of relapsers and non-relapsers.

The five patients with marked EEG abnormalities showed increased side-effects on the Symptom Checklist (15.2 (9.8)), as predicted, compared with the other four patients (5.3 (1.3), $t=-2.26$, one-tailed $P<0.05$), confirming the findings of Johnson *et al* (1970). The lithium, bromine and aluminium levels were slightly lower in the more abnormal EEG group, although not significantly so. A family history of affective disorder was present in three members of the abnormal EEG group and two members of the more normal group.

The levels of trace elements of the three patients whose EEGs showed irregular cortical activity were compared with those of the other six. They had a raised mean (s.d.) bromine level of 7.44 (0.90) μg/ml compared with 6.27 (0.50) μg/ml ($t=-2.57$, two-tailed $P<0.04$). They also had higher mean serum vanadium levels (0.54 (0.10) ng/ml, compared with 0.33 (0.11) ng/ml, $t=-2.71$, two-tailed $P<0.04$). The patients with rhythmic slow activity had normal levels of trace elements.

At the time of the EEG, the group with irregular activity showed no significant difference in their serum lithium levels when compared with the rest of the patient group, nor did those with rhythmic slow activity. When each abnormal group was compared in turn with the rest of the patients, the serum and RBC aluminium levels were found to be similar. In the whole patient group there was no relationship between serum or RBC aluminium levels and estimated general intelligence.

Discussion

We have confirmed the presence of raised bromine levels in patients on long-term lithium treatment, both in the serum and in RBCs. These raised bromine levels correlated with dosage of lithium and with levels of lithium attained in the serum and RBCs. Thus it appears that lithium treatment closely affects endogenous bromine levels.

In view of the above, it is of interest that serum bromine related to retrospective measures of the long-term effectiveness of lithium treatment, and serum lithium levels did not. This finding supports the suggestion of Handorf *et al* (1985) that a rise in endogenous bromine could contribute to the therapeutic effects of lithium. It is interesting that point readings of bromine could relate so well to relapse over a prolonged period, in a relatively small group of patients. Point bromine levels may, therefore, have reflected its mean level over the years, despite possible variations with dose of lithium and dietary intake. We were able to confirm our findings in a prospective study of relapse, which showed a lower endogenous serum bromine level in relapsing patients than in non-relapsing patients. These findings appear worthy of further neurochemical study. Lithium activates the gamma-aminobutyric acid (GABA) system (Hetmar & Nielsen, 1988), and it is possible that bromine enhances the effects of lithium by itself augmenting GABA-ergic functions. Bromine may have this effect by increasing the function of chloride channels linked with GABA and benzodiazepine receptors (Placios *et al*, 1979).

The levels of bromine found in the present study are within the lower range of those relating to EEG abnormalities in methyl-bromide workers in the earliest stages of bromine intoxication. Verberk *et al* (1979) found a geometric mean whole-blood bromine level of 10.9 μg/ml (mean ± s.d. 6.2–19.2 μg/ml) in their group with abnormal EEGs. By comparison, bromine used for medicinal purposes was allowed to build up to considerably higher levels, producing marked toxic effects which were recognised in some patients at a whole-blood level of 500 μg/ml, although six times this level was used by some clinicians and considered not to produce bromism

(Moore *et al*, 1940). There is, therefore, no suggestion from the present study that therapeutic levels of bromine are induced, but it appears that subtle changes in its level or metabolism may be linked with a therapeutic response to lithium.

Levels of aluminium in RBCs are rarely reported, and normative data from dialysis patients were all that were available to us, on which to base our preliminary impressions. In the present study, however, we found aluminium RBC:serum ratios higher than in dialysis patients, not only in the lithium treatment group but also in the normal controls. The lower ratio in renal patients is possibly due to some effect from their higher aluminium levels, or differences in their blood chemistry. Thus lithium treatment was not found to cause any problem with excessive RBC aluminium uptake or raised blood levels. Also, with regard to possible complications of lithium treatment, serum and RBC lithium levels were no higher in patients with the most marked EEG abnormalities, despite their having worse side-effects. It is possible that EEG abnormalities relate to a greater vulnerability to side-effects from lithium.

There are early, inconclusive studies of factors that limit the effects of drugs on the EEG. Manic–depressive patients, receiving lithium and other treatments, appear less likely to have abnormal EEGs if third-ventricular atrophy is present (Dewan *et al*, 1988), or if there is a family history of affective disorder (Cook *et al*, 1986). We do not have tomographic data on our patients, although we have noted that the incidence of family history of affective disorder was similar in patients with or without major EEG abnormalities. The factors promoting EEG abnormalities are doubtless of multifactorial aetiology.

Our EEG findings are tentative, owing to the use of a number of statistical tests in small groups of patients. However, they form a unique pilot study of the neurophysiologically detectable effects of changes in the levels of trace elements during lithium therapy. This is of particular relevance owing to the relation of endogenous bromine to relapse of affective disorder. Although EEG abnormalities were unassociated with lithium levels in serum and RBCs, we found higher levels of bromine and vanadium in a small group of patients showing irregular cortical activity on the EEG. This suggests that the long-term EEG effects of lithium may be mediated, to some extent, through its effects on other trace elements. However, these EEG changes were found in patients who did not have markedly abnormal tracings, so that whatever effects bromine and vanadium may have, appear to be of a limited nature.

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*Norman S. Harvey, MB, ChB, DPM, MRCPsych, MD, *Lecturer in Psychiatry, University of Sheffield, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF*; John Jarratt, MB, ChB, FRCP, *Clinical Neurophysiologist, Royal Hallamshire Hospital, Sheffield*; Neil I. Ward, BSc, MSc(Hon), PhD, *Lecturer in Analytical Chemistry, Chemistry Department, University of Surrey, Guildford, Surrey*